

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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| Date of mailing (day/month/year) 17 July 2001 (17.07.01) | From the INTERNATIONAL BUREAU To: Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE in its capacity as elected Office |
| International application No. PCT/US00/26192 | Applicant's or agent's file reference 15280-4051PC |
| International filing date (day/month/year) 22 September 2000 (22.09.00) | Priority date (day/month/year) 24 September 1999 (24.09.99) |
| Applicant LEPPLA, Stephen, H. et al | |

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:

20 April 2001 (20.04.01)

 in a notice effecting later election filed with the International Bureau on:

2. The election was was not

made before the expiration of 12 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---------------------------------|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorizing officer H Zhou |
| Facsimile No. (41-22) 730 14 84 | Telephone No. (41-22) 338 83 38 |

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference 15280-4051PC | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/US 00/ 26192 | International filing date (day/month/year) 22/09/2000 | (Earliest) Priority Date (day/month/year) 24/09/1999 |
| Applicant THE GOVERNMENT OF THE UNITED STATE OF AMERICA, ... | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

3

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/00/26192

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/32 C07K19/00 C07K14/25 A61K39/07 A61K48/00
A61K39/108

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|----------|--|----------------------|
| X | US 5 677 274 A (NICHOLS PETER J ET AL) 14 October 1997 (1997-10-14) column 1, line 9 - line 17 column 3, line 27 - line 31 column 4, line 12 - line 19 column 10, line 5 -column 11, line 60 --- | 1-24 |
| A | US 5 817 771 A (BAYLEY HAGEN ET AL) 6 October 1998 (1998-10-06) figure 10 column 8, line 7 - line 40 example 3 --- | 1-24 -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Special categories of cited documents .

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

18 June 2001

Date of mailing of the international search report

25/06/2001

Name and mailing address of the ISA

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340 2040, Tx 31 651 epo nl.
Fax (+31-70) 340 3016

Authorized officer

van Klompenburg, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/26192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|----------|--|----------------------|
| A | LIAW L ET AL: "FUNCTIONS OF THE EXTRACELLULAR MATRIX AND MATRIX DEGRADING PROTEASES DURING TUMOR PROGRESSION" BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, BR, RIBEIRAO PRETO, vol. 32, no. 7, July 1999 (1999-07), pages 805-812, XP000872134 ISSN: 0100-879X page 809 -page 810 --- | 1-3,6-9, 23,24 |
| A | MAZAR ET AL: "High-affinity, small cyclic peptide urokinase plasminogen activator receptor (uPAR)-targeting ligands localize reporter and therapeutic conjugates to the surfaces of tumor cells and stimulated endothelial cells" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, PHILADELPHIA, PA: AACR, vol. 40, March 1999 (1999-03), page 22 XP002131000 abstract ----- | 1,4,5, 23,24 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/26192

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---|------------------|
| US 5677274 | A 14-10-1997 | US 5591631 | A | 07-01-1997 |
| | | AT 169959 | T | 15-09-1998 |
| | | AU 682500 | B | 09-10-1997 |
| | | AU 6392294 | A | 29-08-1994 |
| | | CA 2155514 | A | 18-08-1994 |
| | | DE 69412593 | D | 24-09-1998 |
| | | DE 69412593 | T | 18-02-1999 |
| | | EP 0684997 | A | 06-12-1995 |
| | | ES 2122257 | T | 16-12-1998 |
| | | WO 9418332 | A | 18-08-1994 |
| <hr/> | | | | |
| US 5817771 | A 06-10-1998 | AU 4457296 | A | 24-07-1996 |
| | | WO 9620688 | A | 11-07-1996 |
| | | US 5777078 | A | 07-07-1998 |
| | | US 5824776 | A | 20-10-1998 |
| | | CA 2160909 | A | 10-11-1994 |
| | | EP 0753071 | A | 15-01-1997 |
| | | JP 9500102 | T | 07-01-1997 |
| | | WO 9425616 | A | 10-11-1994 |
| <hr/> | | | | |

PATENT COOPERATION TREATY

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REC'D 27 NOV 2001
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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|---|--|---|
| Applicant's or agent's file reference 15280-4051PC | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US00/26192 | International filing date (day/month/year) 22/09/2000 | Priority date (day/month/year) 24/09/1999 |
| International Patent Classification (IPC) or national classification and IPC C07K14/32 | | |
| Applicant THE GOVERNMENT OF THE UNITED STATE OF AMERICA, ... | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 18 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 20/04/2001 | Date of completion of this report 23.11.2001 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Young, C Telephone No. +49 89 2399 7877 |



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/US00/26192

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

2,4,5,9-19,21-33, as originally filed
36-38,41,42,46,47,
49-54

1,3,6-8,20,34,35, as received on 20/04/2001 with letter of 20/04/2001
39,40,43-45,48,
55

Claims, No.:

9-21 as originally filed
1-8,22-24 as received on 20/04/2001 with letter of 20/04/2001

Drawings, sheets:

1-17 as originally filed

Sequence listing part of the description, pages:

1-8, filed with the letter of 21.3.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/US00/26192

- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application.
 - claims Nos. 1-22.because:
 - the said international application, or the said claims Nos. 1-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/26192

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
 - restricted the claims.
 - paid additional fees.
 - paid additional fees under protest.
 - neither restricted nor paid additional fees.
2. This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - complied with.
 - not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - all parts.
 - the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|--------------|
| Novelty (N) | Yes: | Claims 1-24 |
| | No: | Claims |
| Inventive step (IS) | Yes: | Claims |
| | No: | Claims 1-24 |
| Industrial applicability (IA) | Yes: | Claims 23,24 |
| | No: | Claims |

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/26192

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following document:

D1: US-A-5 677 274 (NICHOLS PETER J ET AL) 14 October 1997 (1997-10-14)
D2: US-A-5 817 771 (BAYLEY HAGEN ET AL) 6 October 1998 (1998-10-06)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1 to 22 pertain to a method of targeting a compound to a cell which encompasses both in vitro and in vivo methods. The latter being explicitly excluded from patentability under certain patent systems.

For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of these claims is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1

A method of targeting a compound to a cell over expressing a matrix metalloproteinase. (claims 1-24)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/26192

Invention 2

A method of targeting a compound to a cell over expressing a plasminogen activator (claims 1-24)

Invention 3

A method of targeting a compound to a cell over expressing a plasminogen activator receptor (claims 1-24)

They above inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The subject-matter of the above claims is not inventive (see the grounds for this objection below). The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the claimed subject-matter.

However, this Authority chooses not to invite the Applicant to restrict or request additional examination fees and international preliminary examination will be carried out on the entire application according to Rule 68.1 PCT

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty is acknowledged for claim 1 and consequently all dependant claims thereof.

Inventive step

The closest prior art is represented by D1. Therein a method of killing HIV infected cells using mutant protective antigen is disclosed (see column 36 of D1). The latter being so modified so as to contain a HIV protease cleavage site resulting in the activation of protective antigen on HIV infected cells

The present application differs from D1 in that the cleavage site is a matrix metalloproteinase or a site recognized by plasminogen activator or a plasminogen activator receptor.

The objective problem is defined as;

"to provide a method of killing cells possessing high matrix metalloproteinase or plasminogen activator activity"

The closest prior art discloses a method to kill cells possessing HIV protease activity as described above. The current invention adapts this method for cancer cells which are known to overexpress matrix metalloproteinase and/or plasminogen activators and consequently to be useful targets, see D2 top of column 13. The solution to the objective problem being the exchange of an HIV protease cleavage site for a metalloproteinase or plasminogen activator cleavage site. This would be obvious to the skilled person when faced with the teachings of D2 and the method of D1. Thus, claim 1 does not contain an inventive step within the meaning of Article 33 (3) PCT. The specification of the exact type of matrix metalloproteinase or plasminogen activator or for that matter the exact cleavage sequence or cell type does not warrant acknowledgment of inventive step as these are in themselves merely routine possibilities open to the skilled person in light of what is known about these enzymes in the prior art. Thus, it is considered that all claims suffer from the aforementioned deficiency and as such do not meet the requirements of Article 33 (3) PCT.

Re Item VIII

Certain observations on the international application

Claim 24 refers back to the method of claim 23. However, claim 23 is not a method but rather a product claim. This inconsistency renders the claim unclear and as such said claim is not in compliance with Article 6 PCT.

Claim 1, 23 and dependant claims thereof refer to both protective antigen protein and lethal factor. It is understood from the description that these proteins are part of the anthrax toxin. However no mention of this is made in the claims. As such the claims are unclear and do not conform with the requirements of Article 6 PCT.

WO 01/21656 A2



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.